REMARKS

Upon entry of this Amendment, Claims 1, 4-9, 17-19, 23-25, 30-45, 47-59 and 61-64 will be pending. Claims 1, 4, 5, 6, 8, 17-19, 23, 24, 30, 32, 42, 44, 47, 50-52, 55, 56, 59 and 61 have been amended to more clearly define the present invention. Claims 2, 3, 10-16, 20-22, 26-29, 46 and 60 have been cancelled without prejudice or disclaimer. New claims 62-64 have been added.

Regarding the Amendments

Claims 1, 4 and 5 have been amended to indicate that the claimed antisense oligonucleotide can inhibit tumor cell growth. Support for this amendment can be found throughout the application as filed including, for example, at page 34, line 22 to page 35, line 6 and at pages 42 to 44 (Examples 3 and 4). Claim 4 has been further amended to indicate that the claimed vector comprises "a sequence encoding" an oligonucleotide. Support for this amendment can be found, for example, at page 23, lines 13-15.

Claims 6, 8, 23, 24, 47, 50, 52 and 55 have been amended to indicate that the antisense oligonucleotide is between about 20 and 50 nucleotides in length. Support for this amendment can be found throughout the specification as filed including, for example, at page 15, lines 25 to 27. Claims 8, 24, 50 and 55 have been further amended to remove reference to non-elected subject matter (e.g., SEQ ID NOs). Claims 17-19, 32, 42, 44, 51, 56, 59 and 61 have also been amended to remove reference to non-elected subject matter (e.g., SEQ ID NOs). New claims 62-64 have been amended to indicate that the oligonucleotide is between about 20 and 50 nucleotides in length. Support for this amendment can be found as indicated above.

The foregoing amendments are made without any intention to abandon the subject matter of the claims as filed, but with the intention that claims of the same, lesser, or greater scope may be pursued in the present application or in a continuation, continuation-in-part, or divisional application. It is submitted that the amendments do not

require a new search or consideration because the amendments merely cancel subject matter or clarify the claimed subject matter and do not change the subject matter under consideration. The amendments do not add more claims than were finally rejected and place the claims in condition for allowance, or in better condition for appeal. As such, it is respectfully requested that the amendments be entered.

In Regard to the Advisory Action Mailed January 27, 2005

It is alleged in the Advisory Action mailed January 27, 2005 that the proposed amendments to claims 1, 4 and 5, and new claims 62 to 64 submitted by the Applicant in response to the final Office Action filed with the USPTO on January 5, 2005 introduce new § 112, first paragraph issues of enablement and written description. The Examiner acknowledges that the specification describes the *in vitro* inhibition of expression and tumor cell growth following administration of SEQ ID NOs: 1-3, 5, 6, 8-12 and inhibition of tumor growth *in vivo* in mice following systemic administration of SEQ ID NO: 2. It is alleged, however, that it is unclear, without undue experimentation, which sequences other than SEQ ID NO: 2 inhibit tumor growth *in vivo*. In addition, the Examiner alleges that, while the specification teaches a reduction in metastases in mice following administration of metastatic cells previously transfected *in vitro* with SEQ ID NO: 2 and antisense oligonucleotide GT13611, this is not correlative or representative of the ability to prevent metastasis *in vivo* comprising the administration of antisense oligonucleotides to tumor cells *in vivo*.

With regard to the Examiner's allegation that it is unclear, without undue experimentation, which sequences other than SEQ ID NO: 2 inhibit tumor growth *in vivo*, Applicant respectfully disagrees. The instant specification clearly describes the claimed antisense oligonucleotides, methods for the preparation, isolation and purification of same and methods for evaluating the ability of these antisense oligonucleotides to inhibit tumor growth *in vivo* (see, for example, Example 3). Applicant asserts, therefore, that the one skilled in the art having reference to the instant specification could readily identify,

without undue experimentation, antisense oligonucleotides other than SEQ ID NO: 2 targeted to human neuropilin mRNA that are capable of inhibiting tumor growth *in vivo*, as claimed. Applicant respectfully directs the Examiner's attention to MPEP. § 2164.06, which clearly indicates that, with respect to the enablement requirement under 35 U.S.C. §112, first paragraph, a considerable amount of experimentation may be employed without it being considered undue: "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni,* 195 USQ 150, 153 (CCPA 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 USPA2D 1400, 1404 (Fed Cir. 1988) [Emphasis added]. As discussed above, the instant specification provides clear teaching with respect to the preparation and testing of the claimed antisense oligonucleotides. Furthermore, methods for the preparation and *in vivo* testing of antisense oligonucleotides were well known in the art at the filing date of the instant application. Applicant maintains that, not only does the instant specification provide sufficient guidance with respect to the experimentation required to practice the invention as claimed, but also that this type of experimentation was routine in the art. A worker skilled in the art, therefore, would not consider such experimentation to be "undue."

For the reasons set forth above, Applicants submit that claims 1, 4 and 5, and new claims 62 to 64, submitted in the response filed with the USPTO on January 5, 2005 comply with 35 U.S.C. §112, first paragraph.

With regard to the Examiner's allegation that the teaching in the specification is not correlative or representative of the ability of the antisense oligonucleotides to prevent metastasis *in vivo*, Applicant respectfully disagrees. Applicant maintains for the reasons previously made of record (see, for example, Applicant's previous communications filed on March 28, 2001, April 29, 2002, June 16, 2003 and February 26, 2004) that the specification is fully enabling for a method of inhibiting the metastasis of human tumors

in vivo using antisense oligonucleotides directed against a human neuropilin mRNA. In order to expedite prosecution of the instant application, however, Applicant has cancelled claims 10-13 and dependent claims 46 and 60 without prejudice or disclaimer. Applicant reserves the right to pursue the cancelled subject matter in a divisional, continuation or continuation-in-part application.

Rejection under 35 U.S.C §112

Pursuant to the Office communication mailed August 5, 2004, the Examiner has rejected claims 6-13, 23-25, 30, 45, 46-50, 52-58 and 60 under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement over the scope claimed, for the reasons set forth in the Office Actions mailed January 15, 2003 and August 26, 2003.

It is acknowledged in the Office Action that the specification is enabling for a method of inhibiting human tumor growth *in vivo* (and inhibiting tumor cell growth *in vitro*) comprising the administration of antisense oligonucleotides of 20 nucleotide base lengths that specifically target and inhibit neuropilin expression. The Examiner alleges, however, that the instant disclosure is not enabling with regard to a method of inhibiting human tumor growth comprising the administration of antisense oligonucleotides of larger size range (e.g. 50-100 nucleotides). The Examiner further alleges that the instant disclosure is not enabling with regard to a method of inhibiting the metastasis of human tumors *in vivo* comprising the administration of antisense oligonucleotides *in vivo*.

Applicant respectfully traverses this objection. Applicant asserts that the specification is fully enabling for a method of inhibiting human tumor growth comprising the administration of antisense oligonucleotides of the claimed size range. The instant specification provides considerable teaching for the preparation, isolation and purification of the claimed antisense oligonucleotides. Applicant maintains that the ability of antisense oligonucleotides of 20 nucleotides in length targeted against neuropilin mRNA to effectively inhibit tumor growth *in vivo,* as demonstrated in the instant specification, is predictive of the efficacy of antisense oligonucleotides of larger size targeted against

neuropilin mRNA and that a skilled technician, following the teaching provided in the instant specification, could readily formulate such antisense oligonucleotides for administration to a human. Accordingly, Applicant maintains that one skilled in the art would be able to practice the instant invention without undue experimentation. In order to expedite prosecution of the instant application, however, and without conceding to the correctness of the Examiner's position, Applicant has amended claims 6, 8, 23, 24, 47, 50, 52 and 55 to specify that the antisense oligonucleotides range from about 20 to 50 nucleotides in length. Support for these amendments can be found throughout the specification as filed, for example, at page 15, lines 25 to 27.

With regard to claims 10-13, currently on file, Applicant maintains for the reasons set forth in Applicant's previous communications filed on March 28, 2001, April 29, 2002, June 16, 2003 and February 26, 2004, that the specification is fully enabling for a method of inhibiting the metastasis of human tumors *in vivo* using antisense oligonucleotides directed against a human neuropilin mRNA. In order to expedite prosecution of the instant application, however, Applicant has cancelled claims 10-13, and dependent claims 46 and 60, without prejudice. Applicant reserves the right to pursue the cancelled subject matter in the present application or in a divisional, continuation or continuation-in-part application.

Applicant asserts that the amended claims meet the requirements of 35 U.S.C. §112, first paragraph, and respectfully requests withdrawal of this rejection.

Prior Art Rejection

Pursuant to the Office communication mailed August 5, 2004, the Examiner has rejected claims 1, 4, 5, 31, 33-41 and 43 under 35 U.S.C §103(a) as being unpatentable in light of He *et al.* in view of Milner *et al.* and Baracchini *et al.* The Examiner alleges that it would have been obvious to one of ordinary skill in the art to inhibit the expression of SEQ ID NO:33 using antisense oligonucleotides *in vitro* because the nucleotide sequence of human neuropilin had been taught previously by He *et al.* and the methods of

inhibiting a target gene of known sequence using antisense had been taught previously by Milner *et al.*

The Examiner further alleges that the motivation to study the role of neuropilin in neurite outgrowth and organogenesis can be found in the teachings of He *et al.* and that the teachings of He *et al.*, combined with the routine use of antisense oligonucleotides for inhibiting target gene expression, render the instant invention obvious to one of ordinary skill in the art of molecular biology.

The Examiner stated that the arguments set forth in Applicant's previous communication of February 26, 2004 are not fully persuasive and alleges that there is no particular need to link tumor growth to neuropilin, as stated by Applicant, since the obviousness rejection addresses antisense compositions, not methods of inhibiting tumor growth.

Applicant respectfully traverses this objection. When applying 35 U.S.C. 103, the claimed invention must be considered as a whole (MPEP § 2141). "In delineating the invention as a whole, we look not only to the subject matter which is literally recited in the claim in question... but also to those properties of the subject matter which are inherent in the subject matter *and* are disclosed in the specification" (MPEP § 2141.02) (underlined emphasis added). When considering the instant invention as a whole, one of the inherent properties of the claimed antisense oligonucleotides that is specifically disclosed in the specification is the ability of the antisense oligonucleotides to inhibit tumor growth by inhibiting the expression of neuropilin. This property of the antisense oligonucleotides is, therefore, a feature relevant to the "as a whole" inquiry. "From the standpoint of patent law, a compound and all of its properties are inseparable" (*In re Papesch*, 315 F.2d 381).

As indicated in Applicant's previous communication, nothing in the cited prior art teaches or even suggests a role for neuropilin in tumor cell growth. "Obviousness cannot be predicated on what is not known at the time an invention is made" (*In re Rijkaert*, 9 F.2d 1531). The Examiner suggests that lack of proper regulation of organogenesis can lead to cancer formation (Office Action at page 6, lines 3-4) and alleges that the role of

neuropilin in organogensis is disclosed in He *et al.* However, He *et al.* mention only that ectopic expression of neuropilin (i.e. an overexpression of protein) in mice results in abnormalities of the heart and limbs and that this suggests that neuropilin may have a role in organogenesis. No such role had actually been established. Accordingly, there is nothing in He *et al.* to suggest that neuropilin may be involved in cancer, nor to suggest that inhibition of neuropilin expression at the nucleic acid level may be effective in inhibiting tumor cell growth.

Moreover, Applicant maintains that the Examiner has failed to establish that there is any suggestion or motivation in the cited primary reference of He *et al.*, or in the knowledge generally available to the skilled technician, to modify the reference or to combine reference teachings as is required in order to establish a *prima facie* case of obviousness under 35 U.S.C. 103 (MPEP § 2143). "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination" (MPEP § 2143). The Examiner is respectfully reminded that, when applying 35 U.S.C. 103, the prior art reference also must be considered as a whole (MPEP § 2141).

When viewed as a whole, He *et al.* teaches a human neuropilin in the context of elucidating *in vitro* the mechanisms and pathway by which the Sema III protein mediates its effects on axons of the developing nervous system. In this context, He *et al.* employed an anti-neuropilin antiserum, which acts on neuropilin at the protein level, to further investigate Sema III function and binding to neuropilin. Applicant asserts that He *et al.* does not teach or suggest that Sema III function and binding to neuropilin could be investigated by inhibiting expression of neuropilin at the nucleic acid level through the use of antisense oligonucleotides. In fact, He *et al.* suggests that further binding studies, which would require the presence of a neuropilin protein, need to be conducted in order to elucidate further the role of this protein in the semaphorin pathway (see page 747, right hand column to page 748, left hand column). He thus teaches away from inhibiting the expression of neuropilin protein, since in He's model, insufficient neuropilin protein

would not facilitate a measurable effect arising from the application of anti-neuropilin serum against such protein.

Applicant submits that nothing in Milner *et al.* or Baracchini *et al.* cures the fundamental defects of He *et al.*, as discussed above. Neither Milner *et al.* nor Baracchini *et al.* suggest the instantly claimed antisense oligonucleotides, which are capable of inhibiting tumor cell growth through inhibition of neuropilin expression.

Accordingly, Applicant asserts that one skilled in the art having reference to He *et al.*, Milner *et al.* and Baracchini *et al.*, alone or in combination, would not, at the time the instant application was filed, have been motivated to design antisense oligonucleotides against a human neuropilin mRNA. In addition, such an artisan would not have a reasonable expectation of success in using such antisense oligonucleotides to modulate neuropilin expression and thereby inhibit tumor growth. Furthermore, Applicant respectfully draws the Examiner's attention to amended claim 1, in that none of the cited references teach or even suggest the *in vivo* activity of antisense oligonucleotides against neuropilin in a human.

For the reasons discussed above, Applicant maintains that the Examiner has failed to discharge his burden to establish a *prima facie* case of obviousness and, therefore, respectfully requests that this objection be withdrawn.

In order to more clearly define the instant invention, Applicant has amended claims 1, 4, 5, 31, 33-41 and 43 to indicate that the claimed antisense oligonucleotide is "capable of inhibiting tumor cell growth in a human." Support for these amendments can be found throughout the specification as filed, for example, at page 34, line 22 to page 35, line 6 and at pages 42 to 44 (Examples 3 and 4). Applicant strongly asserts that these amendments have been made for reasons of clarity only and not for reasons of patentability.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this case.

Please charge any additional fees, or make any credits, to Deposit Account No. 07-1896.

Respectfully submitted,

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